Pharmaceutical Research, Vol. 24, No. 2, February 2007 (© 2006)
DOI: 10.1007/s11095-006-9142-y

Research Paper

Mechanistic Investigation of Drug Release from Asymmetric Membrane Tablets: Effect of Media Gradients (Osmotic Pressure and Concentration), and Potential Coating Failures on *In Vitro* Release

Mary Tanya am Ende[1,2] and Lee A. Miller[1]

Received March 11, 2006; accepted July 31, 2006; published online December 19, 2006

Purpose. An asymmetric membrane (AM) tablet was developed for a soluble model compound to study the *in vitro* drug release mechanisms in challenge conditions, including osmotic gradients, concentration gradients, and under potential coating failure modes. Porous, semipermable membrane integrity may be compromised by a high fat meal or by the presence of a defect in the coating that could cause a safety concern about dose-dumping.

Methods. The osmotic and diffusional release mechanisms of the AM tablet were independently shut down such that their individual contribution to the overall drug release was measured. Shut off of osmotic and diffusional release was accomplished by performing dissolution studies into receptor solutions with osmotic pressure above the internal core osmotic pressure and into receptor solutions saturated with drug, respectively. The effect of coating failure modes on *in vitro* drug release from the AM tablet was assessed through a simulated high-fat meal and by intentionally compromising the coating integrity.

Results. The predominant drug release mechanism for the AM tablet was osmotic and accounted for approximately 90–95% of the total release. Osmotic release was shutoff when the receptor media osmotic pressure exceeded 76 atm. Diffusional release of the soluble drug amounted to 5–10% of the total release mechanism. The observed negative *in vitro* food effect was attributed to the increased osmotic pressure from the high fat meal when compared to the predicted release rates in sucrose media with the same osmotic pressure. This suppression in drug release rate due to a high fat meal is not anticipated to affect *in vivo* performance of the dosage form, as the rise in pressure is short-lived.

Conclusions. Drug release from the AM system studied was determined to be robust to varying and extreme challenge conditions. The conditions investigated included varying pH, agitation rate, media osmotic pressure, media saturated with drug to eliminate the concentration gradient, simulated high fat meal, and intentionally placed film coating defects. Osmotic and diffusional shut off experiments suggest that the mechanism governing drug release is a combination of osmotic and diffusional at approximately 90–95% and 5–10%, respectively. In addition, the coating failure mode studies revealed this formulation and design is not significantly affected by a high fat meal or by an intentionally placed defect in the film coating, and more specifically, did not result in a burst of drug release.

KEY WORDS: asymmetric membrane tablets; controlled release; *in vitro* performance; intentional defects in coating; osmotic and diffusional drug delivery.

INTRODUCTION

A review of the patent literature on osmotic drug delivery devices illustrates the innovation and forethought that has been given to this field (1). Inventions vary from complex systems with multiple chambers to the sophisticated, yet simple, push–pull device. Although the devices are unique, there are several features in common. For instance, they all include an osmogen, an active pharmaceutical ingredient (API), and a polymeric film coating. The elementary osmotic pump, developed by Alza as the OROS® technology, has a dense, ideally semipermeable film coating, the nature of which is to allow water to permeate through the film coating into the core tablet, but not to allow release of solubilized core material. For this reason, the OROS® technology depends on a laser-drilled orifice to release dissolved or suspended core material. There is not significant diffusional release of drug or core components through the membrane or orifice in a target range from the OROS® tablet. In fact, Theeuwes (2) identified the optimum delivery orifice size (75–274 μm) for the elementary osmotic pump to minimize solute diffusion through the orifice.

Innovations in the osmotic drug delivery field continued in the 1990s by the development of the controlled porosity

[1] Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340, USA.
[2] To whom correspondence should be addressed. (e-mail: mary.t.am.ende@pfizer.com)

osmotic pump tablet (CP-OPT) by Zentner *et al.* (3–5) and Appel and Zentner (6). The main advancement of the CP-OPT compared to the OROS® system was the new design of the semipermeable membrane to contain pores sufficient in size to eliminate the need for laser drilling an orifice. The CP-OPT membrane also contains a pore former and plasticizer. This osmotic dosage form is designed to deliver a drug solution by an osmotic mechanism, therefore limited in application to soluble compounds.

More recently, in the late 1990s, Okimoto *et al.* (7–10) and Stella *et al.* (11) advanced the CP-OPT technology to encompass poorly water soluble compounds that could be solubilized by Captisol™ (sulfobutyl ether-β-cyclodextrin or $(SBE)_{7m}$-β-CD) that serves as both a solubility enhancing agent and an osmotic agent. As reported in the literature, the use of $(SBE)_{7m}$-β-CD enabled the osmotic release from CP-OPT for prednisolone [aqueous solubility 0.2 mg/mL (7)], chlorpromazine [intrinsic solubility 2.74×10^{-6} mol/L (8, 10)], and testosterone [aqueous solubility 0.039 mg/mL (9)]. The CP-OPT porous, semipermeable membranes employ approximately 60% polymer, such as cellulose acetate, approximately 30% pore former, such as sorbitol, and approximately 10% plasticizer, such as polyethylene glycol 400.

The asymmetric membrane (AM) film-coated tablet is a unique embodiment within the field of osmotic drug delivery. The membrane is formed by a phase inversion process and is composed of a several layers of polymer with a network of interconnecting pores (12). The polymer acts as a semipermeable barrier while the interconnected pores provide a path for dissolved core components to exit. A laser-drilled orifice is not necessary in the AM system as required for the OROS® technology, and similar to the CP-OPT. In fact, the entire AM film coating acts as hundreds of preformed delivery orifices. Therefore, the drug release can be adjusted by varying the type and concentration of the pore former present in the semipermeable membrane as well as the membrane thickness (13). Unlike the CP-OPT, in the AM tablet design the porous, semipermeable membrane contains polyethylene glycol in a dual role, serving as plasticizer and pore former. In addition, these membranes are formed during pan coating through a dry phase inversion process.

There are two different process approaches for 'phase inversion' coatings including a wet and dry method (13). Thombre *et al.* (14) utilized a wet method to apply the coating to form asymmetric membrane capsules using a phase inversion process. The dry method, utilized in this investigation, employs pan coating technology and requires no additional capital investment to implement in commercial drug product facilities. The asymmetric membrane produced by these two different coating methods is similar in terms of performance. The membranes are composed of a porous, nonsymmetric substructure with a dense semipermeable membrane on the exterior. The major difference is that the porous substructure produced by the wet phase inversion method is composed of channels to the dense outer layer; whereas the dry phase inversion method forms a network of interconnected pores with varying sizes and a multitude of smaller dense layers.

Two potential AM coating failure modes were examined in this investigation to develop an understanding of *in vitro* performance under challenge conditions. Firstly, a significant reduction in drug release was discovered in certain AM systems when administered following a high fat meal (15). In the case of ethyl cellulose based film-coated AM tablets it was shown that fats and fat digestion products caused swelling of the AM membrane, effectively shutting off drug release by collapsing the porous membrane into a dense film. This membrane structure change could result in osmotic and hydrostatic pressure that has the potential to rupture the membrane and dose dump. Use of cellulose acetate based film coatings has been shown to be resistant to membrane porosity changes in the presence of a high fat and fat digestion products environment. However, it is feasible to produce a poorly designed cellulose acetate AM tablet that results in rupture during *in vitro* testing, for example when a relatively high concentration of swellable excipient is present in the core, or a low concentration of polymer in the coating, and/or a low coating level is applied to the tablet. Due to the safety concern regarding dose dumping in controlled release dosage forms, a portion of this investigation was dedicated to understanding the effect of intentionally placed defects in the film coating on drug release. The defects are meant to represent possible defects from mishandling during manufacture, packaging, or by the patient.

The core components are also important in achieving optimum performance (characterized by a reproducible release profile and pH and agitation-independent release). In addition to the essential osmogen, the core may include a solubilizing agent and a basic or acidic buffer to maintain a specific pH range within the core. These components are also released through the porous, semipermeable membrane during the entire delivery profile. Similar to the CP-OPT, the AM dosage form delivers a solution and was therefore limited in scope to soluble drug compounds. Thombre *et al.* (16) developed an alternative osmotic dosage form design that delivers a suspension instead of a solution. The mechanisms of drug delivery from AM tablets include contributions from both osmotic and diffusional release (13). As the external medium imbibes through the semipermeable membrane, the soluble components of the core dissolve and create an osmotic pressure difference between the core and external environment. This pressure difference causes the dissolved core components to release through the pores of the semipermeable membrane. The diffusional contribution to release is a result of the porous nature of the membrane.

The predominant research that progressed the understanding of viscosity effects on drug release from osmotic dosage forms was conducted by Okimoto and Stella in the 1990s. Their innovative work revealed that the solubilizing agent sulfobutyl ether-β-cyclodextrin, $(SBE)_{7m}$-β-CD, could also function as an osmogen in the controlled porosity osmotic pump tablet (CP-OPT). For this dosage form, the high viscosity of the $(SBE)_{7m}$-β-CD osmogen impacted the rate of drug release because it created a back pressure that suppressed the diffusional delivery rate. As the osmogen concentration and viscosity reduced with time, the predominant osmotic delivery also decreased but was counterbalanced by an increase in the diffusional driving force (11).

Nelson and Shah (17) studied the effect of viscosity on dissolution kinetics of ethyl *p*-aminobenzoate. This investigation utilized a laminar flow cell to study the impact of

Table I. Compositions of 12-Hour and 24-Hour AM Tablet Formulations Used in this Investigation

Item No.	Component	12-Hour formulation (%)	12-Hour formulation (mg/tablet)	24-Hour formulation (%)	24-Hour formulation (mg/tablet)
1	CP-424,391-18[a]	6.5	13.0	6.5	13.0
2	Mannitol	50.0	100.0	50.0	100.0
3	Fumaric Acid	20.0	40.0	20.0	40.0
4	Microcrystalline Cellulose	22.0	44.0	22.0	44.0
5	Magnesium Stearate (pre granulation)	0.5	1.0	0.5	1.0
6	Magnesium Stearate (post granulation)	1.0	2.0	1.0	2.0
Total Core Tablet		100.0	200.0	100.0	200.0
7	Cellulose Acetate	9.0	16.8	10.0	28.5
8	Polyethylene Glycol	3.0	5.6	2.5	7.1
9	Purified Water[b]	19.0	(41.7)	15.0	(39.6)
10	Acetone[b]	69.0	(149.5)	72.5	(191.4)
Total Film Coat		11.2[c]	22.4	17.8[c]	35.6
Total Tablet Weight			222.4		235.6

[a] Based on theoretical bulk potency of 77.1%; actual potency is 76.8%.
[b] Volatile (not present in final dosage form).
[c] Film coating level is expressed as a percent weight of the core tablet.

viscosity inducing agents hydroxypropyl cellulose, sucrose, and glycerol on diffusion. This study revealed that the viscosity inducing agent may impact the solubility of the model compound, which subsequently affected diffusion. Although quite interesting for cases in which the drug release is monitored in the higher viscosity medium, it does not directly translate to the residual analysis procedure used in our investigations which eliminates this artifact.

Two important distinctions must be kept in mind for the AM tablet osmotic pressure studies reported in this manuscript. Firstly, the viscosity of the soluble inner core materials does not impart a significant affect on water viscosity. Secondly, the sucrose used for the high osmotic pressure media studies increased the viscosity of the external media. However, these studies were conducted by analyzing for residual drug remaining in the tablet, not by detection in the sucrose media, so a change in drug solubility in that media is not an artifact to be concerned about since it was not the method of detection.

The present study focuses on the performance of the AM systems and, for the first time, characterizes the osmotic and diffusional release mechanisms, which were independently shut down in order to measure their individual contribution. Release of a soluble drug into receptor solutions at acidic and basic pH and increasing agitation rate are presented. Lastly, the effects of a high fat meal and intentional film coat defects on drug release from cellulose acetate based film-coated AM tablets are reported. The findings from this work show that the AM tablet *in vitro* performance is robust even under extreme conditions.

MATERIALS AND METHODS

Materials

The core and film coat formulations are shown in Table I. All of the core and film coating components were of either pharmaceutical, United States Pharmacopoeia (USP), or National Formulary (NF) grades. CP-424,391 was the model API used in this investigation, manufactured by Pfizer (Groton, CT), and used as supplied. Mannitol (2080, granular) was purchased from SPI Polyols, Inc. (New Castle, DE), fumaric acid from Haarman and Reimer Corporation (Elkart, IN), microcrystalline cellulose (Avicel® PH102) from FMC Corporation (Philadelphia, PA), and magnesium stearate from Mallinckrodt, Inc. (St. Louis, MO). All excipients were used as received. The cellulose acetate (398-10) was purchased from Eastman Chemical (Kingsport, TN), the polyethylene glycol (3350) from Union Carbide Corporation (Charleston, WV), and the acetone from Fischer Scientific (Fairlawn, NJ). Water used in the preparation of the film coating was heat sterilized and supplied in-house.

Methods

Preparation of Dosage Forms

A blend of mannitol, fumaric acid, and microcrystalline cellulose was geometrically diluted with the model API (CP-424,391) over three blending steps using a twin-shell blender (Patterson-Kelley Division, East Stroudsburg, PA). It was then passed through a Quadro Comil (Comil, Model No. 197s, Quadro Engineering Inc., Waterloo, Ontario Canada, impeller: 2A-1607-086; sharp edges; screen: 2A-062H050/68; 0.250 inch spacer) at a speed setting of six. The material was blended again for 20 min. Magnesium stearate was added to the formulation and it was blended for an additional 4 min.

Roller compaction of the formulation was performed using a Freund TF-mini roller compactor (Vector Corporation, Marion, IA) with a roller pressure was 40 kg/cm^2, auger speed was 18–19 rpm, and a roller speed was 6 rpm. The compacted ribbons were milled using a rotating granulator fitted with a 20-mesh screen. Additional magnesium stearate was added and the granulation was blended for 4 min. The granulation was compressed on a Manesty F-press (Manesty Machines, Liverpool, England) tablet press fitted with a 5/16 inch, standard round concave tooling.

The cellulose acetate based film coatings were applied to the core tablets using an HCT-30EP (Vector Corporation, Marion, IA) pan coater. The exhaust temperature ranged

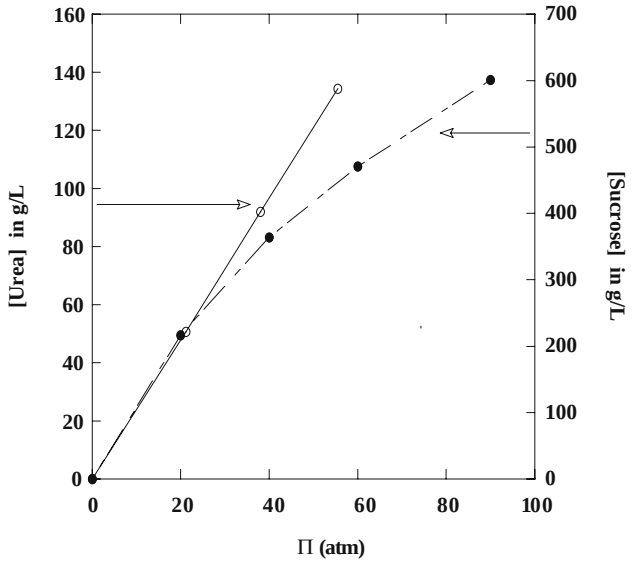

Fig. 1. Effect of urea and sucrose concentration on solution osmotic pressure. Non–linearity in the concentration - osmotic profile determined experimentally by the dilution method is consistent with data listed in CRC Handbook [19], p. D-231, 55th Edition, 1974–1975.

between 24 and 26°C, spray rate was 20 g/min, and pan speed was 20 rpm. The coating level ranged between 11.0 and 18.0 wt% based on the core tablet weight of 200 mg. The coated tablets were dried in the HCT-30EP for 15 min at an inlet temperature set point of 60°C and dried in an oven (Gruenberg solvent tray oven, Gruenberg Oven Company, Williamsport, PA) for 16 h at 40°C.

Two different film-coat formulations were applied to the same core tablet to achieve the desired release rates of 80% in 12 or 24 h. In order to extend the release rate from 12 to 24 h, the ratio of cellulose acetate to polyethylene glycol was increased from 3.0 to 4.0 and the ratio of acetone to water was increased from 3.6 to 4.8. In addition, the two film coat formulations were applied at different film thicknesses and are expressed as percent weight of the core tablet in Table I.

In Vitro Dissolution Test and HPLC Assay

CP-424,391 is a weak base with a pK_a of 7.7 and a solubility range of 5.5 mgA/ml to >100 mgA/ml over a pH range of 7.0 to 1.2, respectively (18). Dissolution studies were conducted in USP type II systems (Hanson Corporation, Chatsworth, CA, rotating paddles, 50 rpm unless otherwise noted, 37°C). The dissolution medium was selected from one of the following: (a) simulated gastric fluid without enzymes at pH 1.2, or SGN, (b) simulated intestinal fluid without enzymes at pH 7.5, or SIN, (c) a simulated high fat breakfast otherwise denoted as meal at pH 6.6. CP-424,391 was assayed by reverse phase high performance liquid chromatography (HPLC) using a fixed volume of 25 µl injected onto the analytical column (Waters Symmetry C8 column 15 cm×3.9 mm diameter) containing 5 µm stationary phase. The mobile phase was composed of perchloric acid, water, and acetonitrile in volume percentages of 0.37:74.63:25.00. The mobile phase was prepared by adding 5 ml of perchloric acid to 1,000 ml distilled water with stirring. Then 750 ml of this aqueous perchloric acid solution was volumetrically measured and added to 250 ml of acetonitrile while stirring. The well-mixed mobile phase was degassed under reduced pressure with continuous stirring or ultrasonic agitation for 5 min. The mobile phase flow rate through the HPLC column was 2.0 ml/min with CP-424,391 UV detection at 210 nm. The dissolution media pH was measured following the dissolution study to ensure consistency during the test period.

Osmotic Release Shut off

Shut off of the osmotic release mechanism was studied by characterizing the AM tablet dissolution profiles over a range of media osmotic pressures by varying the concentration of urea or sucrose in the receptor solution. The osmotic pressure of the solutions was verified by a vapor pressure osmometer (Vapro model 5520, Wescor Inc., Logan, UT) with an upper limit of 81.3 atm (3,200 mOsm/kg). The instrument was calibrated using standards ranging from 2.54 to 25.4 atm (100–1,000 mOsm/kg) prior to and during use. Because the osmotic pressure of some of the receptor solutions was beyond the capability of the instrument, diluted samples were prepared to verify solution osmotic pressure. In addition, there is a known nonlinear dependence of sucrose concentration on osmotic pressure above 35 atm (Fig. 1). A stock solution was prepared and dilutions were assayed to provide a standard curve, which was extrapolated in order to achieve an osmotic pressure at 90 atm. Osmotic pressures of the diluted calibration samples from the stock solution were measured and found to agree with the standard curve and data taken from the *Handbook of Chemistry and Physics* (19).

The same dissolution apparatus was used as described in the previous section. Due to high viscosity of the receptor solution, the percent drug release was determined by residual drug content in the tablet rather than a direct solution sample. The tablets were removed at specific time points (2, 6, 18, and 24 h), rinsed with distilled water, patted dry, cut

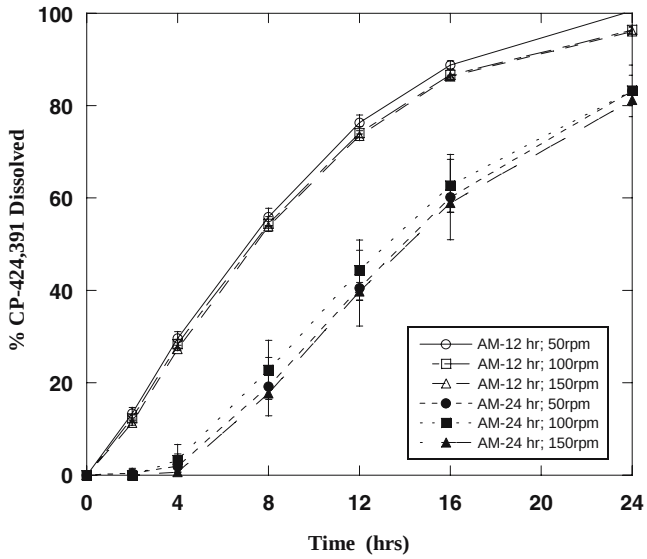

Fig. 2. Effect of agitation rate on CP-424,391 release from 12-hour and 24-hour AM tablets into SIN.

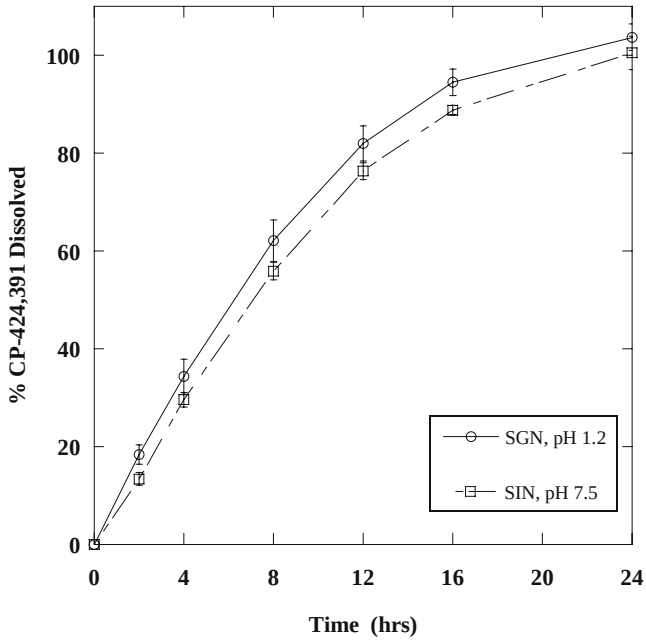

Fig. 3. Effect of media pH on CP-424,391 release from 12-hour AM tablets at 50 rpm.

into quarters (# 11 scalpel, Becton Dickson AcuteCare, NJ), placed into volumetric flasks, and dissolved in distilled water with shaking and sonication. The scalpel was rinsed with distilled water into the flask to capture any material adhering to the blade. Three tablets were assayed per time point via HPLC as described earlier. The drug released was calculated by measuring the residual drug content and subtracting it from the theoretical tablet potency. The resulting value was averaged over the three tablets tested per time point. This method of sample preparation and assay will be referred to as the "residual drug content method." The dissolution media osmotic pressure was measured following the osmotic release dissolution study to ensure consistency during the test period.

The average initial release rates were calculated from 0 to 60% released, the upper bound extended to 80% if the linear least squares regression fit was good (R^2>0.95). For the 12- and 24-h AM tablets of CP-424,391 the release time denotes when approximately 80% drug is released into SIN. The shut off osmotic pressure was determined by establishing a calibration curve of release rates versus media osmotic pressure and extrapolating to 0% released per hour.

Diffusional Release Shut off

Shut off of the diffusional release mechanism was accomplished by characterizing the AM tablet dissolution profile into SIN saturated with CP-424,391. Dissolution was conducted as described in the section *In Vitro* Dissolution Test and HPLC Assay. Saturated drug solutions were prepared by adding 7.6 g of CP-424,391 to 900 ml of SIN at 37°C. The solution pH was maintained at 7.5 in SIN by addition of concentrated NaOH. The tablets were assayed by the residual drug content method.

An experimental challenge in conducting diffusional release shut off studies for highly soluble drug substances was in achieving saturation for the drug in the external dissolution media. An additional constraint was to conserve usage of drug substance during novel testing studies. With these considerations in mind, saturation of drug was achieved by employing a high pH media of SIN at 7.5 in which the drug is least soluble. It is acknowledged here that these conditions do not achieve 100% diffusion release shut down, as there remains a slight concentration gradient across the AM membrane exposed to acidic concentrations of CP-424,391 on the core side and basic concentrations of CP-424,391 on the receptor medium side. The dissolution media osmotic pressure was measured following the diffusional release study to ensure consistency during the test period.

Dissolution Test into Meal

The food effect on drug release from the AM dosage forms was studied by performing dissolution studies into high fat breakfast. Meals were purchased from an area restaurant (International House of Pancakes in Groton, CT) and contained two scrambled eggs (80 g), two slices of bacon (17 g), two pieces of toast (60 g), six ounces of hash brown potatoes (120 g), eight ounces of whole milk (240 ml), and butter (8 g). The individual components from each breakfast were blended using a conventional food processor and combined with 250 ml of USP simulated intestinal fluid with pancreatin (Sigma-Aldrich). The final volume was approximately 770 ml, which provided sufficient media for two 24-h dissolution tests (~385 ml each) at 37°C. Dissolution studies were conducted as described earlier except the agitation rate was increased to 100 rpm. The tablets were assayed by the residual drug content method. The dissolution media osmotic pressure was measured following the high fat meal dissolution study to ensure consistency during the test period.

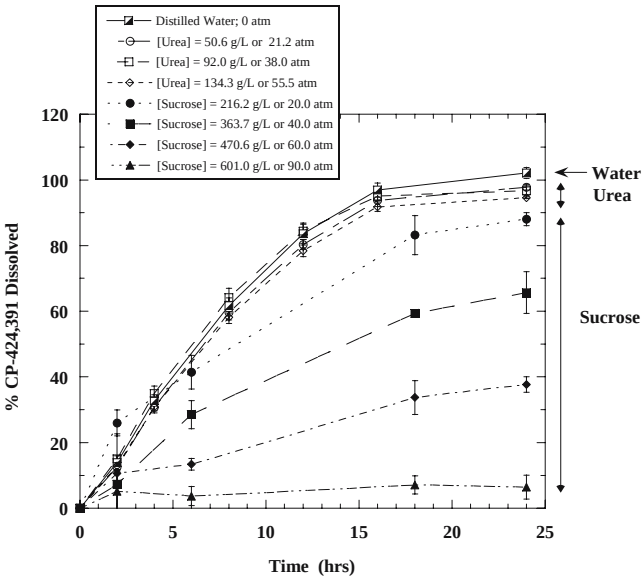

Fig. 4. Effect of external media osmotic pressure (urea and sucrose) on release of CP-424,391 determined by residual drug content method.

Intentionally Placed Membrane Defects

The effect of damage to the film coating on AM tablet performance was evaluated for safety considerations and potential dose dumping. To ensure consistent and reproducible failure of the AM coating, defects were intentionally placed in the dosage forms under this challenge. Defects, in the form of slits, were cut through the film coating in one of four ways. Slits were made on the face of the tablet such that the slit extended either over half of the tablet diameter ($0.5\times D$) or across the entire diameter ($1\times D$). Slits were also made through the membrane over one half of the tablet circumference ($0.5\times C$) either in the land or bandwidth areas. Each tablet received only one slit. Visual observations were made pre- and postdissolution testing under magnification to verify that the cuts penetrated through the tablet film coating.

RESULTS AND DISCUSSIONS

The release rate of CP-424,391 was shown to be independent of agitation rate for both the 12- and 24-h formulations. As shown in Fig. 2 the drug release profile is essentially the same regardless of increased agitation rate from 50 to 150 rpm. In Fig. 3, the release rate of CP-424,391 from the 12-hr AM tablet into SGN and SIN showed only a slight difference in release rate. These results are consistent with osmotic drug delivery systems that exhibit condition-independent release kinetics as a function of pH and agitation.

Effect of Urea or Sucrose as Osmotic Agents

Increased media osmotic pressure using urea was not found to significantly affect the drug release kinetics for the AM coated tablet (Fig. 4). The experiments were repeated and demonstrated to be consistent with initial results. This finding was initially unexpected due to the use of urea as osmotic agent to demonstrate osmotic release of nonporous, semipermeable, film coated dosage forms (4). Therefore, the experiments were repeated and demonstrated to be consistent with the initial results. The distinctive feature for AM tablets is that they are composed of several layers of polymer with a network of interconnecting pores. The asymmetric membrane overall is not ideally semipermeable because the interconnected porous substructure is permeable. The hypothesis to explain our atypical finding that release is unaffected by increased media osmotic pressure using urea is that urea freely permeates the porous semipermeable membrane by convective flow with water and by diffusion. Thus, the osmotic driving force was not affected by having a high concentration of urea in the external media. Although not definitively proven by experimentally measuring the presence of urea in the core contents, this unexpected finding is reported to the scientific community.

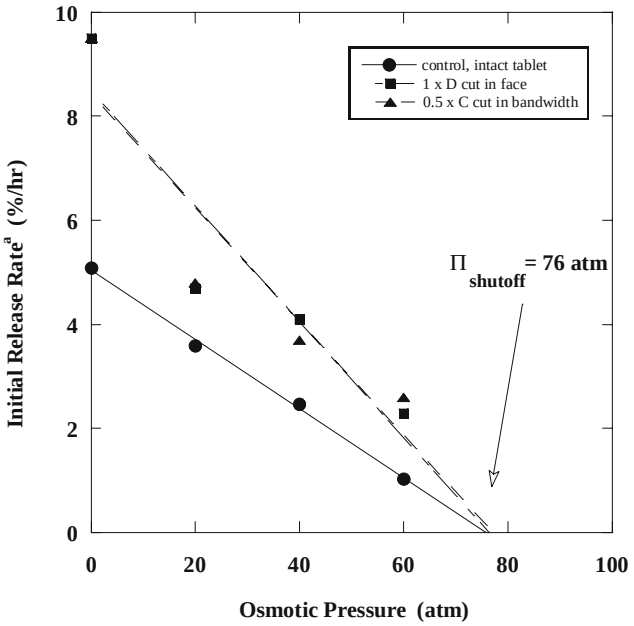

Fig. 5. CP-424,391 release rate from AM tablets as a function of increasing external osmotic pressure due to sucrose concentration in receptor solution. [a]Initial release rate determined by linear regression over 0–60% release profile.

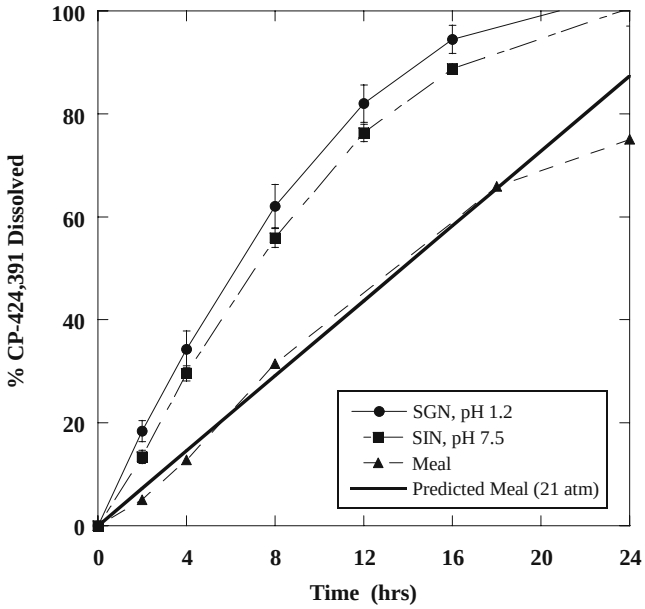

Fig. 6. Effect of dissolution media on CP-424,391 release from 12-hour AM tablets using a USP II apparatus with media at 37°C composed of (i) 900 ml of SGN at 50 rpm; (ii) 900 ml of SIN at 50 rpm; (iii) 375 ml of simulated meal at 100 rpm.

An additional study using sucrose was performed to further improve our understanding of the permeability of AM coating to a relatively high molecular weight agent. Five different dissolution media osmotic pressures (0, 20, 40, 60, and 90 atm) were prepared by varying the concentration of sucrose. In this study, increased osmotic pressure in the external dissolution medium significantly reduced the drug release rate (Fig. 4). Using intact tablet results, extrapolation of the drug release rate to 0%/hour indicated that osmotic release would be completely shut off when the media osmotic pressure exceeded 76 atm (Fig. 5).

The effect of a broad range of osmogens (varying molecular weight and ionization potential) on drug release kinetics from AM coated tablets of varying formulations is necessary to further understand these observations.

Table II. Media Osmotic Pressure and Its Effect on Release Rate

Medium	Osmotic pressure (atm)	Release rate (%/h)
SGN	5.6	6.8[a]
SIN	7.0	6.4[b]
Simulated meal	21.0	3.7[c]
Predicted release at 21.0 atm	21.0	3.6

[a] SGN release rate calculated from n=5 time points, R^2 =0.988.
[b] SIN release rate was calculated from n=5 time points, R^2 =0.994.
[c] Simulated meal release rate was calculated from n=5 time points, R^2 =0.996.

Effect of Simulated Meal on Drug Release

The *in vitro* performance of the AM tablets in the simulated meal was studied to assess potential food effects for cellulose acetate based, film-coated AM tablets. This work was completed based on reports that drug release from ethyl cellulose based film-coated AM tablets was shut down after administration following a high fat meal (15). The data shown in Fig. 6 revealed suppression of drug release into the simulated meal relative to drug release from AM tablets into SGN and SIN media. However, the mechanism for suppression in this case was different than what was reported to have happened in the ethyl cellulose based system. These results were not attributed to a change in membrane structure, but rather to the high osmotic pressure of the simulated meal, which was measured at 21 atm compared to 5.6 and 7.0 atm for SGN and SIN, respectively. In SGN and SIN the release rates were 6.8 and 6.4%/h, respectively. The release rate from AM tablets into media with 21 atm osmotic pressure was predicted at 3.6%/hr (Table II). The predicted release rate into the meal agrees well with the actual rate of 3.7%/hr determined by *in vitro* dissolution studies.

The release rates were calculated from the initial 60% to 80% of drug release using a linear fit to the data. Therefore, it is not surprising that the predicted meal profile is linear, and this profile deviates from the actual performance in the meal after the initial 60% of drug is released at approximately 18 h. These results are consistent with the method of calculation compared to the actual release profiles for osmotic systems.

These *in vitro* simulated high fat meal results suggest that osmotic pressure from a meal may cause slow drug release. However, *in vivo*, an increase in osmotic pressure of this magnitude from a meal has been shown to be diluted within a period of approximately 1 h (20). Therefore, it is expected that, in practice, AM tablets prepared from cellulose acetate formulations will function independently of food *in vivo*. Although not within the scope of the work reported here, clinical results verified no significant food effect for the 12-h AM tablet of CP-424,391.

Effect of Intentionally Placed Defects on Drug Release

Intentionally placed defects in the AM coating caused a detectable (5–10 percentage units) enhancement in the drug release after 4 h (Fig. 7). The position of the defect appears to have a slight influence on the rate and extent of drug release, being worst for defects located at the band rather than the face or land locations. Most importantly, in all cases,

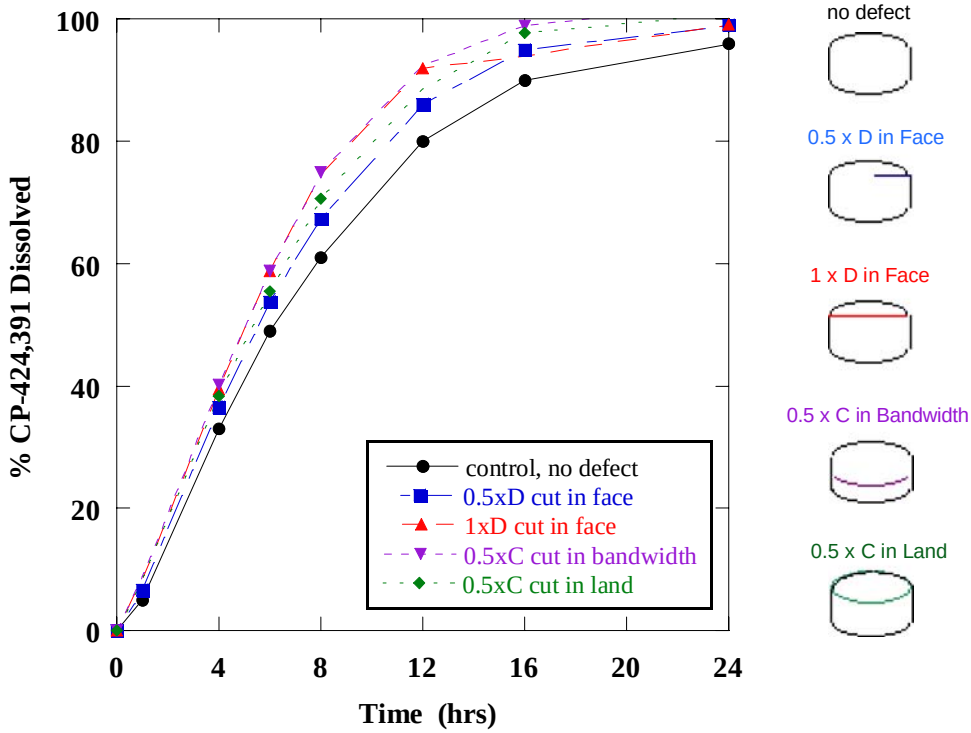

Fig. 7. Effect of intentionally placed defects[a] in the AM coating on drug release into 900 ml of 0.1 N HCl using a USP II apparatus with media at 37°C. [a]The defects placed in locations representing potential weak points, including the face (one–half to one–full diameter, D, in length), the bandwidth (one–half circumstance, C, in length), and the land, or tablet edge (one–half circumstance, D, in length).

the intentional defects do not result in dose dumping as demonstrated by Fig. 7.

The inner core of AM tablets remains essentially intact after dissolution testing based on visual inspection. The defect surface area constitutes less than 10% of the original coated tablet surface area after 24-h dissolution testing (Fig. 8). Based on the theory that osmotic systems are controlled by the water influx, which is affected by coating permeability and surface area, a slight increase in area produced from defects ranging from 0.5 to 1.0 diameter across the tablet does not significantly affect the release. The amount of surface area affected by the defect is much less than the total surface area of the micron-sized drug delivery orifices inherit to the AM film coating. Thus, the device continues to function as an osmotic system even with the slits. The core of the hydrated dosage form exists in multiple phases in the radial axis (i.e., solution at the coating interface, dissolving front, and dry core). However, the inner core may not be a well-mixed

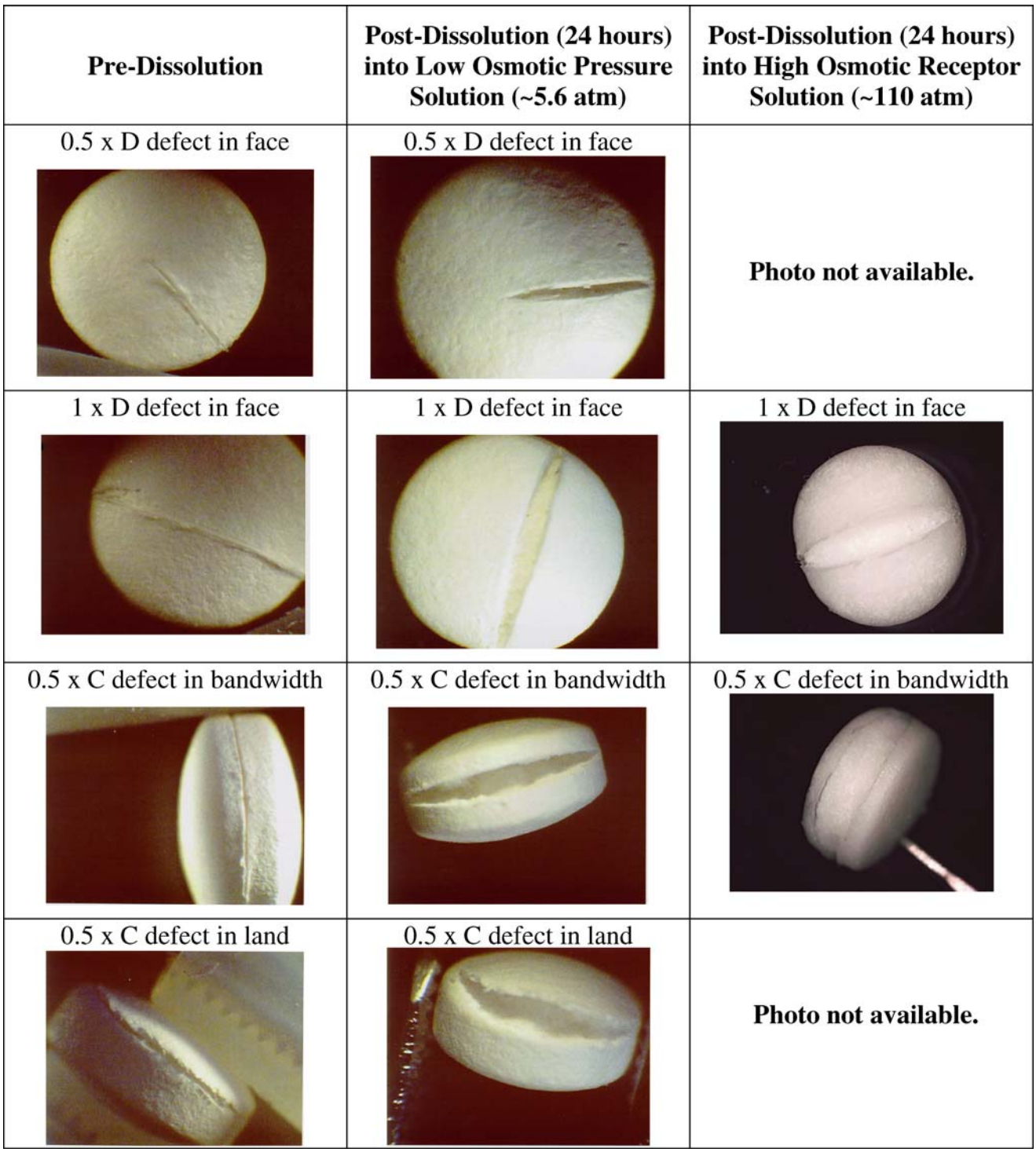

Fig. 8. Pre- and post–dissolution of intentionally defected AM-coated tablets into low and high osmotic pressure solution.

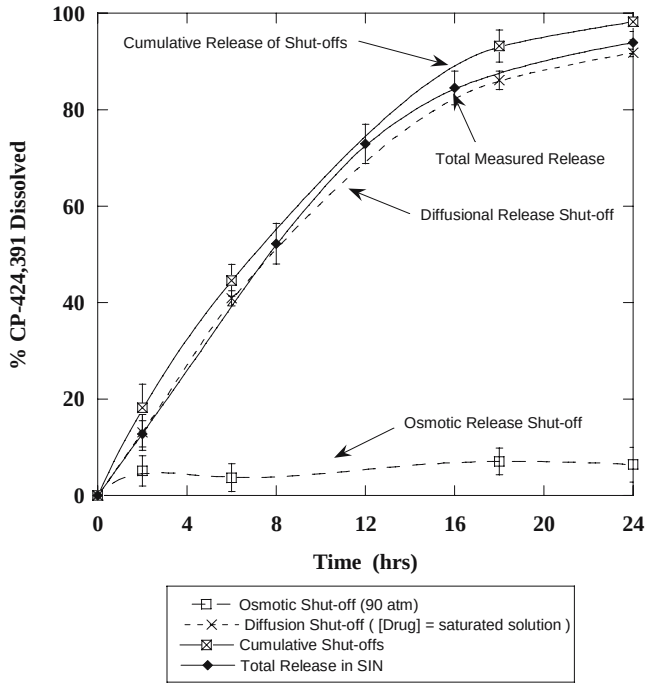

Fig. 9. Comparison of CP-424,391 release rates as a function of release mechanisms (osmotic + diffusional, diffusion only, osmotic only).

compartment axially. Therefore, the solution region would only be affected by a slit (or other loss of film coat integrity) in the immediate vicinity of the breach.

AM tablets with defects located at one full diameter of the face and one half the circumference of the bandwidth were further investigated to prove their condition-dependency on media osmotic pressure. As shown in Fig. 5, the release mechanism remains predominantly osmotic since release can be shut off with increased media osmotic pressure. In fact, the shut off pressure is approximately the same at 76 atm, regardless of the presence of a defect in the coating.

Photographs were taken of the tablets prior to and after dissolution testing for 24 h (Fig. 8). In low osmotic pressure media the postdissolution tested AM tablets with defects on the face and bandwidth reveal that the soluble components have released by 24 h. However, in high osmotic pressure media, these tablets exhibit a slight swelling and an expansion in the defect area compared to tablets exposed to low osmotic pressure media. Under high osmotic pressure conditions the water imbibition rate would be shut off due to the high osmogen content in the media, which in turn shuts off the osmotic release. However, water may enter the tablet through the defect region and release at a rate of approximately 5%/hr by diffusion.

Osmotic and Diffusional Release Mechanisms

Diffusional Release Contribution (Osmotic Shut off)

The major mechanism governing drug release from AM tablets was demonstrated to be osmotic through the use of sucrose in the receptor solution to increase the osmotic pressure (Fig. 4). As depicted in Fig. 5, the dosage form release rate as a function of receptor solution osmotic pressure (due to sucrose) was completely shut off by using media in excess of 76 atm. When tested using media osmotic pressure of 90 atm these AM tablets were found to release drug by a diffusive mechanism at approximately 5% of the total profile, as shown in Fig. 9.

Osmotic Release Contribution (Diffusion Shut off)

Osmotic pressure of the receptor solutions was measured prior to and immediately following dissolution tests and showed no significant increase in osmotic pressure due to release of soluble core material into the media from up to three AM tablets per vessel. The initial and postdissolution media osmotic pressure was measured as 3.7 and 3.8 atm, respectively. The media pH was initially set at 7.5, and was determined to be maintained constant throughout the study, as measured by the final pH of 7.4. The release profile was reduced by approximately 5% in the case of shutting off the diffusional release mechanism. This corroborates well within the 5–10% diffusional release profile determined by the osmotic release shut off experiment depicted in Fig. 9 and, therefore, supports the use of basic-pH conditions to saturate drug concentration in the medium.

Cumulative Release (Osmotic Shut off + Diffusional Shut off)

The drug release mechanisms for the AM tablet were demonstrated by separate experiments using receptor solutions (i) concentrated with sucrose to an osmotic pressure of 90 atm to shut off osmotic release, or (ii) concentrated to saturation for the soluble drug to shut off diffusional release. The cumulative drug release profile was created by the summation of the osmotic shut off and diffusional shut off profiles (Fig. 9). These findings correspond well with the total release of CP-424,391 from AM tablets into SIN.

CONCLUSIONS

The AM system is a unique embodiment within the field of osmotic drug delivery. This work shows that the dosage form performance is robust to varying and extreme conditions. The AM tablet demonstrated condition-independent release kinetics as a function of media pH and agitation, consistent with osmotic delivery devices. Osmotic and diffusional shut off experiments suggest that the mechanism governing drug release is a combination of osmotic and diffusion at approximately 90–95% and 10–5%, respectively.

Coating failure mode studies revealed this formulation and design is not significantly affected by a high fat meal or by an intentionally placed defect in the film coating, and more importantly, did not result in a dose dumping. AM tablets composed of a cellulose acetate-based, semipermeable membrane exhibit a negative *in vitro* food effect that is consistent with an increased osmotic pressure from the meal. This transient affect is not predicted to be significant *in vivo* due to rapid adjustment of osmotic pressure within the gut. This research also demonstrated that even intentionally placed defects as large as one-full diameter in the coatings do not result in dose dumping from CP-424,391 AM tablets. The dissolution performance is proven to be robust to challenging media and defects. For the first time, this study

confirms that the mechanism governing drug release from AM tablets is a combination of osmotic and diffusional at approximately 90–95% and 10–5%, respectively.

ACKNOWLEDGMENTS

The authors wish to extend their gratitude to the following people for their valuable contributions: Dave Fortin, Scott Herbig, Barbara Johnson, Richard Korsmeyer, Paul Luner, Cindy Oksanen, Rusty Poe, Michael Puz, Joseph Stemple, Avi Thombre, and Ken Waterman.

REFERENCES

1. G. Santus and R. W. Baker. Osmotic drug delivery: a review of patent literature. *J. Control. Release* **35**:1–21 (1995).
2. F. Theeuwes. Elementary osmotic pump. *J. Pharm. Sci.* **64**: 1987–1991 (1975).
3. G. M. Zentner, G. S. Rork, and K. J. Himmelstein. The controlled porosity osmotic pump. *J. Control. Release* **1**:269–282 (1985).
4. G. M. Zentner, G. S. Rork, and K. J. Himmelstein. Osmotic flow through controlled porosity films: an approach to delivery of water soluble compounds. *J. Control. Release* **2**:217–229 (1985).
5. G. M. Zentner, G. S. Rork, and K. J. Himmelstein, U.S. Patent 4,968,507 (1990).
6. L. E. Appel and G. M. Zentner. Use of modified ethylcellulose lattices for microporous coating of osmotic tablets. *Pharm. Res.* **8**:600–604 (1991).
7. K. Okimoto, M. Miyake, N. Ohnishi, R. A. Rajewski, V. J. Stella, T. Irie, and K. Uekama. Design and evaluation of an osmotic pump tablet (OPT) for Prednisolone, a poorly water soluble drug, using $(SBE)_{7m}$-β-CD. *Pharm. Res.* **15**:1562–1568 (1998).
8. K. Okimoto, A. Ohike, R. Ibuki, O. Aoki, N. Ohnishi, T. Irie, K. Uekama, R. A. Rajewski, and V. J. Stella. Design and evaluation of an osmotic pump tablet (OPT) for Chlorpromazine using $(SBE)_{7m}$-β-CD. *Pharm. Res.* **16**:549–554 (1999).
9. K. Okimoto, R. A. Rajewski, and V. J. Stella. Release of testosterone from an osmotic pump tablet utilizing $(SBE)_{7m}$-β-cyclodextrin as both a solubilizing and an osmotic pump agent. *J. Control. Release* **58**:29–38 (1999).
10. K. Okimoto, A. Ohike, R. Ibuki, O. Aoki, N. Ohnishi, R. A. Rajewski, V. J. Stella, T. Irie, and K. Uekama. Factors affecting membrane-controlled drug release for an osmotic pump tablet (OPT) utilizing $(SBE)_{7m}$-β-CD as both a solubilizer and osmotic agent. *J. Control. Release* **60**:311–319 (1999).
11. V. J. Stella, V. M. Rao, and E. A. Zannou. The pharmaceutical use of captisol: some surprising observations. *J. Incl. Phenom. Macrocycl. Chem.* **44**(1–4):29–33 (2002).
12. S. M. Herbig, J. R. Cardinal, R. W. Korsmeyer, and K. L. Smith. Asymmetric-membrane tablet coatings for osmotic drug delivery. *J. Control. Release* **35**:127–136 (1995).
13. M. T. am Ende, S. M. Herbig, and R. W. Korsmeyer, Osmotic drug delivery from asymmetric membrane film-coated dosage forms. In D. Wise (ed.), *Handbook of Pharmaceutical Controlled Release Technology*, Marcel Dekker, New York, 2000, pp. 751–785.
14. A. G. Thombre, J. R. Cardinal, A. R. DeNoto, and D. C. Gibbes. Asymmetric membrane capsules for osmotic drug delivery II. *In vitro* and *in vivo* drug release performance. *J. Control. Release* **57**:65–73 (1999).
15. M. B. Chidlaw, D. T. Friesen, S. M. Herbig, J. A. S. Nightingale, C. A. Oksanen, and J. B. West, Controlled-release of an active substance into a high fat environment, WO 2004052343 (2004).
16. A. G. Thombre, L. E. Appel, M. B. Chidlaw, P. D. Daugherity, F. Dumont, L. A. F. Evans, and S. C. Sutton, Osmotic drug delivery using swellable-core technology. *J. Control. Release* **94**: 75–89 (2004).
17. K. G. Nelson and A. C. Shah. Mass transport in dissolution kinetics. I: Convective diffusion to assess the role of fluid viscosity under forced flow conditions. *Pharm. Res.* **76**:799–802 (1987).
18. P. A. Carpino, B. A. Lefker, S. M. Toler, L. C. Pan, J. R. Hadcock, E. R. Cook, J. N. DiBrino, A. M. Campeta, S. L. DeNinno, K. L. Chidsey-Frink, W. A. Hada, J. Inthavongsay, F. M. Mangano, M. A. Mullins, D. F. Nickerson, O. Ng, C. M. Pirie, J. A. Ragan, C. R. Rose, D. A. Tess, A. S. Wright, L. Yu, M. P. Zawistoski, P. A. DaSilva-Jardine, T. C. Wilson, and D. D. Thompson. Pyrazolinone–piperidine dipeptide growth hormone secretagogues (GHSs): discovery of capromorelin. *Bioorg. Med. Chem.* **11**:581–590 (2003).
19. R. C. Weast. *Handbook of Chemistry and Physics 55*. The Chemical Rubber Company, Cleveland, OH, 1974.
20. J. S. Fordtran and T. W. Locklear. Ionic constituents and osmolality of gastric and small-intestinal fluids after eating. *Am. J. Dig. Dis.* **11**:503–521 (1966).